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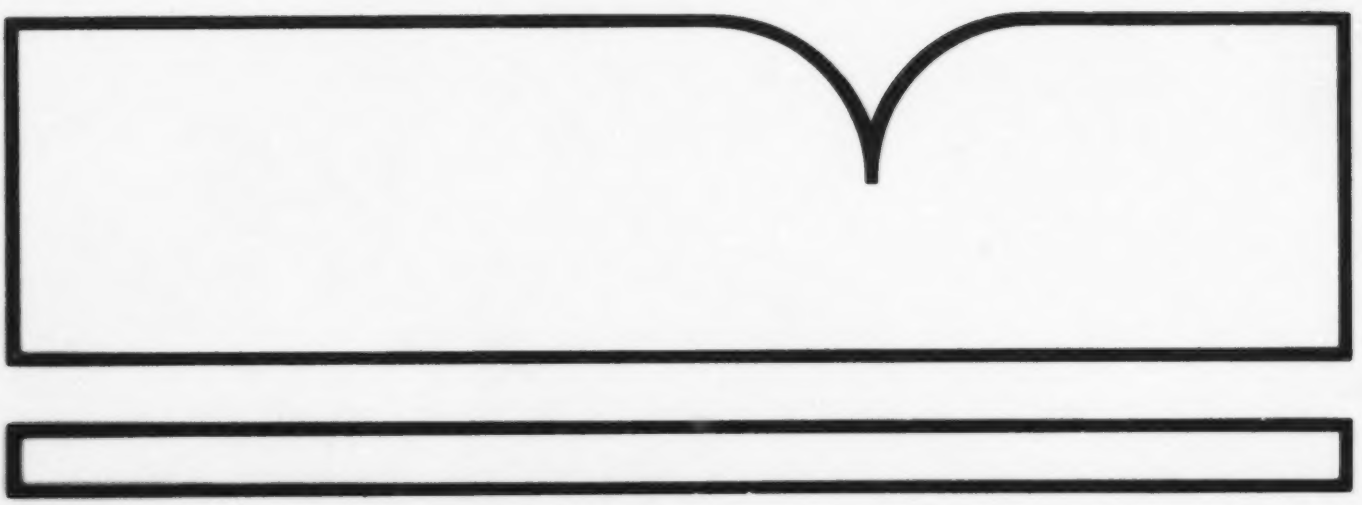

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16. ABSTRACT

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The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progress, Issues, and Research Strategies

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ABSTRACT. In Xuan Wei, a rural Chinese county of about one million people, females' annual lung cancer mortality is China's highest, and males' is among China's highest. Xuan Wei's very high indoor air pollution levels (sometimes exceeding 20 mg/m³), residentially stable population, relatively uncomplicated lifestyle, and wide geographic variation in lung cancer mortality render it highly amenable to quantitative, interdisciplinary investigation of chemical carcinogens due to indoor air pollution. To date, epidemiologic findings reveal a closer association of lung cancer with the indoor burning of "smoky" coal (as opposed to "smokeless" coal or wood) than with tobacco use or occupation. Current aerometric, chemical, and toxicologic findings tend to confirm this association, though the specific carcinogenic constituents of Xuan Wei indoor air pollution have not yet been determined. Chinese and American investigators are conducting interdisciplinary field and laboratory investigations to quantify the lung cancer risk attendant on indoor air pollution relative to other factors, to measure and compare the characteristics of pollution from different Xuan Wei fuels, to determine the relative etiologic importance of pollution composition and concentration, and to develop quantitative relationships between air pollution dose and lung cancer risk.

XUAN WEI COUNTY, in northeastern Yunnan Province, China, is 6,257 km² and lies on high plateau punctuated by mountain ridges. Its total population is about one million people, over 90% of whom belong to China's predominant ethnic group, the Han. Xuan Wei is rural—over 90% of residents are farmers—and until the 1980s was relatively untouched by modernization. Nonagricultural occupations include homemaking, coal mining, office work, and industrial work in chemical fertilizer plants, two coal-fired electric power plants (including one of Yunnan's largest), and a cement products plant. All of these plants were built after 1960.

Xuan Wei has 20 communes with populations of about 30,000 to 60,000. Each commune is divided into

"large production teams," of which there are 385 in the County. Each large team is further divided into 15 to 25 "small production teams." The population is residentially stable; fewer than 20% of households experienced in- or out-migration from 1965 to 1985. Xuan Wei is well known for its export of ham, though the typical local diet consists of corn, potatoes, rice, and about 400 g of unsmoked pork per week.

Tobacco smoking is very rare in Xuan Wei females but common in males. Factory-made cigarettes and locally grown tobacco are used. Cigarettes are frequently smoked through water pipes. Tobacco is seldom used orally or nasally. For generations, Xuan Wei residents have used three major fuel types, "smoky" coal, "smokeless" coal, and wood, for home heating and cooking. Smoky coal is glossy black, has a low sulfur content, and smokes heavily on firing. Smokeless coal is dull black, has high sulfur and ash contents, and produces little smoke. Because smokeless coal is powdery, it is usually mixed with clay to form briquets prior to burning.

Most Xuan Wei residents live in mud-brick or wooden two-story homes in which the cooking, dining, and living area is downstairs and the sleeping area is upstairs. The average household contains about five people, including children, parents, and often grandparents. Women generally start the domestic fire in the morning and prepare the two or three daily meals eaten at home, while men spend most daylight hours outside the home. Females generally start cooking at about age 12. Domestic fuel has traditionally been burned in a shallow, unvented pit in the floor of the dwelling's main room.

Lung cancer in Xuan Wei

Annual unadjusted and adjusted lung cancer mortalities in China, the U.S., Yunnan Province, and Xuan Wei are presented in Table 1.[1] In the Table, as throughout this report, the term "lung cancer" includes carcinomas of lung, bronchus, and trachea. During 1973–1975, males' and females' lung cancer mortalities in Yunnan Province were 19th and 25th, respectively, among China's 29 provinces, municipalities, and autonomous regions.[2] In marked contrast, females' rates in Xuan Wei were higher than in any other Chinese county, and males' rates were among China's highest. Males' and females' absolute mortalities were similar, a surprising finding in view of the rarity of smoking in women. In the Chinese national cancer survey of 1973–1975, lung cancer was the only type of cancer for which mortality in Xuan Wei exceeded the national average. Of 115 tumor specimens examined pathologically in Xuan Wei, 58% were squamous cell carcinomas, 28% were adenocarcinomas, and the remainder were mixed cell, undifferentiated, or alveolar carcinomas.[3]

The marked difference in lung cancer mortality among Xuan Wei communes was especially striking. This difference is apparent in Table 1, and Figure 1 shows a map of Xuan Wei County with commune boundaries, annual unadjusted lung cancer mortalities in each commune, and locations of mines supplying smoky and smokeless coal for domestic use. That commune population denominators are reasonably large, and that vigorous lung cancer surveillance is conducted throughout the County, strongly suggest that

Table 1.—Annual Lung Cancer Mortality Rates in China and the U.S.

Place and time period	*Lung cancer mortality rate, per 100,000*					
	Unadjusted		Age-adjusted to 1964 China population		Age-adjusted to 1970 U.S. population	
	Males	Females	Males	Females	Males	Females
China 1973–1975	5.0*		6.8	3.2	12.3	5.7
U.S. 1970	53.7	12.0	30.0	6.3	53.7	12.0
Yunnan Province 1973–1975	2.8*		4.3	1.5	6.9	2.5
Xuan Wei County 1973–1979	27.0	24.5	27.7	25.3	43.2	38.7
Three Xuan Wei communes of highest lung cancer mortality (Cheng Guan, Lai Bin, Rong Cheng) 1973–1979	114.4	120.6	118.0	125.6	186.8	193.4
55–59 yr age group in high-mortality communes	849.4	904.0				
Three Xuan Wei communes of low lung cancer mortality (Pu Li, Yang Liu, Re Shui) 1973–1979	4.0	2.8	4.3	3.1	5.8	4.3
55–59 yr age group in low-mortality communes	17.1	18.1				

*Unadjusted rate for both sexes combined.

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the observed intercommune variation in lung cancer mortality is real.

On balance, Xuan Wei constitutes a very unusual natural experiment in lung cancer production. The marked local variation in the dependent variable (lung cancer mortality) presents a rare opportunity to investigate the relative etiologic roles of independent variables (known and suspected risk factors). That such important independent variables as population mobility and lifestyle are reasonably well "controlled" further enhances Xuan Wei as a setting for quantitative, interdisciplinary investigation of lung cancer etiology. Since the 1970s investigators from Beijing and Yunnan Province have conducted epidemiologic, aerometric, toxicologic, and chemical studies in Xuan Wei. In 1982 they were joined by investigators from the U.S. Environmental Protection Agency.

Overview of current evidence

Data gathered to date in Xuan Wei disclose a stronger association of lung cancer with domestic coal use than with any other risk factor so far assessed, including tobacco smoking. As shown in Figure 1, in communes with smoky coal mines (including Cheng Guan [CG] and Rong Cheng [RC], most of whose residents use smoky coal from Lai Bin [LB] commune), the average annual lung cancer mortality in 1973–1975 was 35 per 100,000, in contrast to an average of 4 per 100,000 in communes without smoky coal mines. Also, in 1982 Chinese investigators conducted a survey of fuel use and tobacco smoking in 11 Xuan Wei communes. The proportion of households in each commune using smoky coal before 1958 was highly correlated with commune-specific lung cancer mortality between 1973 and 1975 ($r = 0.82$, $p = .002$).

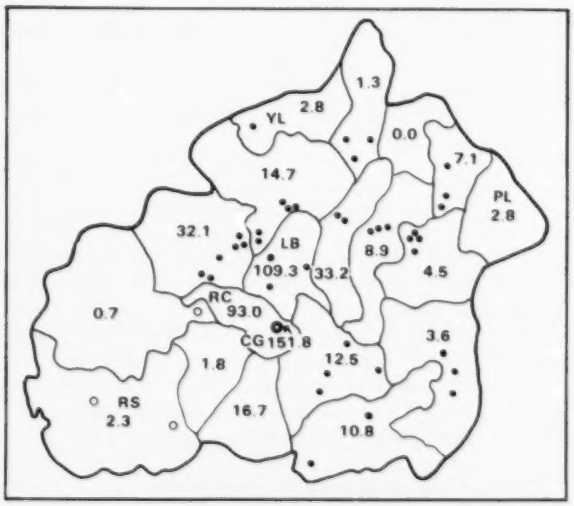

Fig. 1. Map of Xuan Wei County, showing commune boundaries, each commune's unadjusted annual lung cancer mortality rate per 100,000 (both sexes, 1973–1975), and mines supplying domestic coal: (●) smoky coal and (○) smokeless coal. Designated communes: CG, Cheng Guan; LB, Lai Bin; PL, Pu Li; RS, Re Shui; RC, Rong Cheng; and YL, Yang Liu. (*Science* 1987, 235:217–220. Copyright 1987 by the AAAS. Reprinted with permission.)

Table 2 shows 1982 survey results for two Xuan Wei communes, LB and Re Shui (RS), with very different lung cancer mortality rates. Sex-specific smoking habits differed little between the two communes (indeed, somewhat more males had smoked in RS), but fuel use habits differed greatly, with nearly all of LB, and none of RS, using smoky coal. In a previous survey,[3] higher lung cancer rates were detected in farmers than in coal miners or office workers, tending to exclude nonagricultural occupations as an important lung cancer risk factor.

In 1983, indoor air was sampled in Xuan Wei homes in which smoky coal, smokeless coal, and wood were burned. Concentrations of particulates and total organics (dichloromethane-extractable portion of particulate samples) were measured. Total organic samples and chemical fractions thereof were also subjected to Ames testing (Tables 3 and 4). Extremely high levels of particulates and total organics were observed in homes burning smoky coal and wood (Table 3); levels during smokeless coal burning were considerably lower

Table 2.—Results of 1982 Survey of Smoking and Fuel Use in Two Xuan Wei Communes with High and Low Lung Cancer Mortality Rates

	Commune	
	Lai Bin	Re Shui
Population	60,000	60,000
Unadjusted annual lung cancer mortality rate per 100,000 1973–1975	109.3	2.3
Percentage of population ever smoking tobacco		
Males	44.02%	49.05%
Females	0.05	0.07
Percentage of population using		
Smoky coal	89.7%	0.0%
Smokeless coal	1.6	33.4
Wood	8.7	66.6

Table 3.—Mean Indoor Air Pollution Levels (mg/m³) in Xuan Wei, 1983, by Type of Fuel Burned

	Suspended particulates* (mg/m³)	Dichloromethane-extractable organics (mg/m³)
Smoky coal (Cheng Guan)	24.4	17.6
Smoky coal (Lai Bin)	9.5	7.8
Wood (Re Shui)	22.3	12.3
Smokeless coal (Re Shui)	1.8	0.5

*Suspended particulates as measured by high-volume sampler with an air flow rate of 40 ft³/min, equipped with a head designed to exclude half of particles of 10 μm diameter.

Table 4.—Ames Test Mutagenic Potency of Total Organics and Organic Fractions* of Xuan Wei Indoor Air Pollution, 1983, by Type of Fuel Burned

	Potency (revertants × 1000 per mg of sample)			
	Smoky coal (Cheng Guan)	Smoky coal (Lai Bin)	Wood (Re Shui)	Smokeless coal (Re Shui)
Total organic sample	2.6	3.3	0.9	2.6
Organic fractions				
Aliphatic	0	0	0	0
Aromatic	2.1	3.2	3.4	2.5
Moderately polar	1.4	2.4	2.6	3.0
Polar	4.0	5.6	0.5	2.0

*Organic fractions were extracted with different solvents, as follows: aliphatic, hexane; aromatic, hexane/benzene; moderately polar, dichloromethane; polar, methanol.

(though still high by U.S. standards). Levels of individual polycyclic aromatic hydrocarbons, including benzo(a)pyrene, were generally highest during smoky coal burning, intermediate during wood burning, and lowest during smokeless coal burning. In the smoky and smokeless coal samples, most organics were in the aromatic (hexane/benzene-extractable), moderately polar (dichloromethane-extractable), or polar (methanol-extractable) fractions. Aliphatic (hexane-extractable) concentrations were relatively low for all fuel types.

The Ames test mutagenicity (revertants per cubic meter of air) of total organic combustion samples from smoky coal was considerably higher than that of smokeless coal or wood samples.[1] The mutagenic potency (revertants per milligram of sample) of organic smoky and smokeless coal samples was higher than that of wood samples (Table 4). The potency of the polar fraction was highest in smoky coal combustion samples and lowest in wood samples, but the potency of each of the other organic fractions did not differ greatly among the three fuel types. On balance, differences in mutagenic potency among the fuel types were not as great as differences in lung cancer mortality among the communes using the different fuel types.

A case-control study is currently in progress in Xuan Wei. In this study each lung cancer patient is matched for age and sex with a control subject whose residence is selected randomly from throughout the County. Interim findings from the first 39 case-control pairs of females and 33 pairs of males are presented in Tables 5 and 6. Among females, there were no smokers 10 yr prior to the study. Among males, the majority of cases and controls had been smokers (Table 5), leaving few discordant pairs for consideration. At the same time, the number of controls smoking heavily, 21, was larger than the corresponding number of cases, 15. These observations suggest that smoking may not be as serious a lung cancer risk factor in Xuan Wei as in numerous other locations.

If length of using smoky coal were positively associated with risk of lung cancer, one would expect the odds ratio associated with smoky coal use to increase with increasing remoteness in the time at which smoky coal was used. In the interim case-control distributions,

Table 5.—Interim Distribution of Cigarette Smoking 10 yr Prior to Study in 33 Male Case-Control Pairs in Xuan Wei

	Cases		
	Not smoke	L.E. 16 cigarettes/day	>16 cigarettes/day
Controls			
Not smoke	2	0	2
L.E. 16 cigarettes/day	0	6	2
>16 cigarettes/day	3	7	11

Table 6.—Interim Odds Ratios Associated with Smoky Coal Use Now, 20 yr Ago, and at Age 12 in Xuan Wei Lung Cancer Patients and Controls

Time using smoky coal	Males (33 pairs)	Females (39 pairs)
Now	1.5	2.6
20 yr ago	1.3	2.9
At age 12	4.0	3.7

such a trend was observed in both sexes (Table 6). However, the absolute magnitudes of the odds ratios were not as great as might have been expected in light of evidence summarized above. Because females customarily spend much more time than males near the domestic fire, one might expect smoky coal-associated ratios to be substantially higher in females; in fact, the interim odds ratios did not differ greatly by sex.

Epidemiologic issues and research goals

Though available findings reveal a definite relationship between smoky coal use and lung cancer in Xuan Wei, the relationship is by no means fully characterized as yet. It will be necessary to gather further information on four interrelated levels. The first-level goal is to quantitate the importance of smoky coal use relative to

other known and suspected risk factors. On this level, several important questions must still be addressed. For example, the unexpectedly small odds ratios associated with smoky coal use and small etiologic impact of tobacco smoking remain to be confirmed and explained.

The second-level goal is to determine the similarities and differences among the combustion products of fuels, including different smoky coals, used in different Xuan Wei communes. While communes with smoky coal mines generally have higher lung cancer rates than communes without them, rates vary greatly even among communes with smoky coal mines. This variation is probably not fully explained by historical differences in fuel use from commune to commune. Instead, it appears probable that the generic term "smoky coal" encompasses a set of coals which differ geographically in composition and combustion products, and whose combustion products may confer different risks of lung cancer. Indeed, the observed differences in pollution levels during smoky coal combustion in CG and LB communes (Table 5) suggest that different smoky coals vary in at least the concentrations of their combustion products.

The third-level goal is to determine and compare the etiologic importance of the dose (or concentration) and chemical/physical composition of indoor air pollution in Xuan Wei. It is conceivable that certain Xuan Wei coals produce lung cancer because their combustion products contain carcinogens not found elsewhere in the County. It is also possible that the composition of different coals' combustion products is similar, and that lung cancer is related primarily to differences in pollution dose emitted by different coals. Of course, risk may well be a complex function of both composition and concentration. The observed similarity in mutagenic potency between smoky and smokeless coal combustion products (Table 4) suggests that pollution concentration is an etiologically important factor, but by no means eliminates the possibility that Xuan Wei coals exhibit important differences in composition.

The fourth-level goal is to develop quantitative relationships between pollution dose and the likelihood of developing lung cancer. Such relationships will maximize the contribution of the project to the risk assessment process. The most appropriate functional form of these relationships cannot be determined until the relative etiologic importance of indoor air pollution and other risk factors is known, until combustion products of different Xuan Wei fuels have been more fully characterized and compared, and until the relative importance of pollution composition and concentration has been more thoroughly assessed.

Research strategies

To exploit fully the learning opportunities offered by the Xuan Wei project, Chinese and American investigators have mounted an interdisciplinary research program to accomplish project goals. The program incorporates epidemiology, environmental measurement, chemistry, and toxicology. Field and laboratory investigations are closely linked. In addressing the different goals, the various disciplines are employed as described below.

In addressing the first-level goal, determination of the etiologic importance of domestic fuel use relative to other risk factors, epidemiology assumes the major role. Cross-sectional questionnaire surveys and a case-control study are being conducted. The main purpose of the cross-sectional surveys is to measure and compare the distributions of fuel use and other risk factors in communes with different lung cancer mortalities. Survey results will allow qualitative inference as to the relative importance of the risk factors. For instance, the observation that factors other than fuel use were distributed similarly in high- and low-mortality communes would tend to underscore the etiologic importance of fuel use.

The case-control study is intended to quantitate the etiologic importance of fuel use relative to other risk factors. Lung cancer patients and controls, selected as described above, are queried in detail about fuel use history, tobacco use history, occupational history, socioeconomic status, diet, family medical history, and other factors. Logistic regression will be employed to determine the adjusted lung cancer risk attendant on each of the factors studied.

All disciplines are closely integrated to accomplish the second-, third-, and fourth-level research goals described above. Field and laboratory investigations are both used to compare the compositions and concentrations of fuel combustion products. Laboratory conditions have been designed to simulate field conditions as closely as possible. Field studies allow direct linkage of environmental measurements to epidemiologic information. Laboratory studies allow more detailed measurement of combustion products, including short-lived and volatile species, than can be performed in the field.

In the Xuan Wei project, pollution samples collected in the field and the laboratory are often subjected to toxicologic assay. Comparison of biologic activities yields clues as to the relative etiologic importance of combustion products from different fuels. Toxicologic assay of different chemical fractions also allows inference as to the relative etiologic importance of pollution composition and concentration. Furthermore, toxicologic testing provides an assessment of the relative ability of different types of assay to predict human experience with lung cancer.

The results of first-, second-, and third-level investigations will all contribute to the development of quantitative relationships between air pollution dose and lung cancer response. First-level studies are expected to identify epidemiologic covariates that must be considered in the construction of dose-response functions. The reliability and specificity of these functions will depend largely on the outcome of second- and third-level studies. For example, these studies may show that the combustion products of various Xuan Wei fuels are chemically and physically similar, and differ only in the concentrations of pollutants generated. If so, dose-response functions may be reliable but not specific as to the relative etiologic impact of individual pollution constituents. On the other hand, if pollution composi-

tion and concentration are both shown to vary across different Xuan Wei fuels, it may be possible to develop dose-response functions that are both reliable and specific. In any event, the Xuan Wei project is expected to generate new and useful evidence as to the influence of indoor air pollution on lung cancer production.

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